

Role of Itraconazole Pulse Therapy with Adjuvant Isotretinoin in treating Recurrent and Recalcitrant Dermatophytosis

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ABSTRACT

Introduction: Dermatophytosis are the most common skin diseases affecting millions of people of Bangladesh. Increased number of recurrent and recalcitrant dermatophytosis are now-a-days an emerging public health problem in our daily practice. Mono therapy with oral antifungals leads to partial clearance or relapse of lesions. Isotretinoin due to its keratolytic effect used as an adjuvant to oral antifungals for recalcitrant dermatophytosis. In the absence of susceptibility tests and studies, it is difficult to comment whether these recurrences represent true resistance to common antifungals or are due to other reasons.

Objectives: This is a prospective, randomized study to assess the effectiveness of oral monthly pulse dose of Itraconazole with daily low dose of isotretinoin in the treatment of recurrent and recalcitrant superficial dermatophytosis

Methods: A total of 40 patients with positive KOH and previous history of treatment with antifungals were included in this study. All the patients received the same antifungal Itraconazole 200 mg twice daily for 7 days in each month for 3 months with additional adjuvant daily dose of 20 mg isotretinoin for the same duration. The patients were followed up at 2, 3 and 6 months from baseline for signs of relapse.

Results: Clinical cure and mycological cure from baseline were very promising and significant.

Conclusion: Itraconazole Pulse therapy with adjuvant Isotretinoin daily can be an effective in treating relapsing & recalcitrant superficial dermatophytosis.

KEYWORDS: Dermatophytosis, relapsing, Itraconazole, Isotretinoin

INTRODUCTION

Dermatophyte infections are common worldwide, and dermatophytes are the prevailing causes of fungal infection of the skin, hair, and nails.¹⁻³

The term superficial dermatophytosis refer to the fungal infection of keratinised tissues including the stratum corneum of the epidermis, hair, nails and horny tissue of animals.⁴

A diagnosis of a cutaneous dermatophyte infection may be strongly suspected based upon the clinical findings. However, testing to confirm the diagnosis is recommended because a variety of cutaneous disorders may present with

similar features. A potassium hydroxide (KOH) preparation is a rapid method to confirm the diagnosis.

It needs to be treated because of long term morbidity but in present era the treatment is challenging because of recurrences and/or relapses. Topical treatment with different topical antifungals have a limited role especially in adult population. Older systemic medications like Griseofulvin, ketoconazole and terbinafine are associated with low cure rates and a potential of side effects adverse drug interactions.⁵ On the other hand, newer antifungals like itraconazole

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have higher cure rates and fewer adverse reactions but still there are relapses that we are facing in our daily practice. So, there emerges a need to have some effective adjuvant which reduces the time duration of oral antifungals and also takes care of recurrences and relapses. In this study we added oral isotretinoin due to its keratolytic effects as an adjuvant to oral antifungals for recalcitrant dermatophytosis.

METHODS

The study was conducted in the Department of Dermatology & Venerology of Community Based Medical College, Bangladesh, Mymensingh after approval from the ethical committee.

Inclusion criteria

In this study 40 recurrent and relapsed cases of dermatophytosis patients were included. Patients of Tinea cruris and Tinea corporis with >30%BSA and duration of infection ≥ 3 months with positive KOH preparation were recruited between January 2018 to December 2018.

Exclusion criteria

- BSA $\leq 30\%$
- Infection within 3 months
- Severe systemic disease
- Pregnancy and lactation
- Immunosuppressive state of patients
- Age ≥ 60 years

Informed consent was obtained from all patients prior to their enrollment. Details of duration and progression of the disease, treatment taken, occupation and other co morbidities were obtained in all patients and general physical and systemic examination were carried out. The percentage of body surface area involved and duration of infection were recorded. The worst

affected area was selected as a target area.

Severity of infection was assessed on the basis of erythema, pruritus and scaling on 4 point scale (0,1,2,3). On each of the three parameters: no, mild, moderate and severe. Then the three scores of target area were added to get a clinical assessment score (CAS). Baseline investigation including CBC, LFT, RFT, and pregnancy test in eligible formats were done in all patients. Photographic documentation was done at baseline and at every follow up visit.

Eligible patients were given oral itraconazole 200mg twice daily for 7 days in each month for 3 months. All the patients also received topical vaseline. Patients were followed up after 1,2,3 months during treatment and after treatment. Total scores were recorded at each visit.

Over all clinical improvement was also graded at each visit on 4 point scale (global assessment index) both by patient and physician as follows:

- <25% improvement: Poor
- 26-50 % improvement: average
- 50-75% improvement : good
- >75% improvement: excellent

Efficacy of treatment was assessed on the following parameters at 1 month, 2 month and 4 months

1. **Clinical cure:** Completely normal appearing skin with no residual changes.
2. **Mycological cure:** Negative KOH microscopy.
3. **Relapse:** Positive KOH preparation or clinical worsening at least 8 weeks after a negative KOH or clinical improvement/ cure had been achieved.

Compliance with treatment as well as tolerability and side effects of the drug were also assessed at each visit.

RESULT

Table 1 shows characteristics of the studied dermatophytosis patients, it is noted that 52.5% of the patients were in the 31-40 year age group. At the same time, 65.0% of the patients were males (26). More than half (55.0%) of the patients had a moderate form of the disease and 35% had a severe form. Most of the patients were farmer (32.5%). All the patients were either relapsed cases, or had recurrent disease, with 40% of the relapse cases having received multidrug antifungal therapy.

In our study, at the end of 2 months, clinical effectivity was achieved in 36 (90%) patients and mycological cure achieved in 38 (95%) patients. After the follow up period of 2 months, 6 (15%) patients relapsed.

None of the patient developed any hematologic or biochemical abnormalities.

Characteristics of the studied patients

Age in years	Total number of patients (N=40)	Percentage of patients
21-30	11	27.5
31-40	21	52.5
41-50	08	20

Sex	N = 40	Percentage
Male	26	65
Female	14	35

Occupation	N = 40	Percentage
Farmer / Labor	13	32.5 %
Housewife	10	25 %
Service	07	17.5 %
Business	06	15 %
Student	04	10 %

Previous Drug history	N = 40	Percentage
Fluconazole	08	20 %
Terbinafin	06	15 %
Itraconazole	06	15 %
Griseofulvin	03	7.5 %
Ketoconazole	01	2.5 %
Multidrug	16	40 %

Outcome of Treatment	N = 40	Percentage
Clinical Cure	36	90 %
Mycological Cure	38	95 %
Relapse	06	15 %

DISCUSSION

Dermatophytosis is one of the commonest skin problem in Bangladesh with the highest incidence in tropical countries having higher temperatures and high humidity. Many antifungals are being used for complete cure, but success often are not being achieved. Itraconazole is a triazole antimycotic agent with strong keratophilic and lipophilic properties. Similar to other azole antifungal agents, the mode of action of Itraconazole involves inhibition of 14- α -demethylase, resulting in impaired sterol synthesis in fungal cell membrane.

In an attempt to explore adjuvant treatment in recalcitrant dermatophytosis, isotretinoin was found to be good to reduce the recurrences and/or relapses. However, the mechanism of action of isotretinoin is not fully understood, but we can draw clues from the pathogenesis of dermatophyte infection and effect of isotretinoin on human skin.

A pilot study was conducted by Rashmi Arora &

Apeksha Solanki in Gujrat India with Itraconazole alone and in combination with isotretinoin. In which, they showed better outcome with isotretinoin. A total of 76 eligible patients with KOH positive superficial dermatophytosis were allocated to two groups. Both groups were given oral itraconazole 100mg BD with topical antifungals (Clotrimazole) for 15 days. After 2 weeks one group was continued with same line of treatment and second group received oral isotretinoin 0.3 & 0.4 mg/kg/day, in addition after normal baseline investigation.⁶

Retinoids act as modulators of epidermal growth and supervisors of differentiation. Although they act toward normalization in hyper proliferative epithelia as in psoriasis; in normal epidermis, they promote cell proliferation.² Therefore, increased cell turnover in the epidermis may halt the spread of ongoing infection by eliminating the growing dermatophyte.

Following adherence, successful installation of dermatophytes requires rapid germination of arthroconidia and penetration of hyphae into the stratum corneum. Failure to do so will result in elimination by the continuous desquamation of the epithelium.⁷

Dermatophytes work optimally at acidic pH and the skin being acidic gives an ideal ambient environment for the fungus.⁸ High transepidermal water loss and impaired barrier function of the skin are correlated with high skin PH.⁹ On being treated with retinoid therapy, the skin pH is raised, thereby possibly inhibiting the growth of dermatophytes.

Retinoids are also known for their keratolytic effect. They reduce the corneocyte cohesiveness and also alter terminal differentiation of epidermis.⁴

Finally Retinoids stimulate humoral and cellular immunity, enhance antibody production and stimulating peripheral blood T helper cells which counteract the immunosuppressive effect of dermatophyte.⁴

However, we do not recommend oral isotretinoin for the routine treatment of dermatophytes but it will act as good adjuvant in treating recalcitrant dermatophytosis.

REFERENCES

1. Havlickova B, Czaika VA, Friedrich M. Epidemiological trends in skin mycoses worldwide. *Mycoses* 2008; 51 Suppl 4:2.
2. Seebacher C, Bouchara JP, Mignon B. Updates on the epidemiology of dermatophyte infections. *Mycopathologia* 2008; 166:335.
3. Ameen M. Epidemiology of superficial fungal infections. *Clin Dermatol* 2010; 28:197.
4. Verma S,heffmanm,superficial Fungal Infection.in Wolff Et Al ;editor ;fitzpatrick *Dermatology In General Medicine*,7th Edition;ch.no.-188; 1807-21.
5. Orfanos CE, Zouboulis CC, Almond-Roesler B, Geilen CC. ,Current use and future potential role of retinoids in dermatology. *Drugs* 1997; 53:358-88.
6. Rashmi Arora and Apeksha Solanki; Comparative efficacy of monotherapy of oral Itraconazole with oral Itraconazole with Isotretinoin in chronic and/or resistant superficial dermatophytosis : *INDIAN JOURNAL OF RESEARCH* Vol-7 (6) June-2018:10-13.
7. Martinez-Rossi NM, Peres NT, Rossi A. Antifungal resistance mechanisms in dermatophytes. *Mycopathologia* 2008;166:369-83. 2. Ogawa H, Summerbell RC, Clemons KV, Koga T, Ran YP, Rashid A, et al. Dermatophytes and host defence in cutaneous.
8. Brasch J,zaldua M.enzyme Patterns Of Dermatophyte. *mycoses* 1994; 37:11-6.
9. Thune P,nilsen T,hanstand Ik, Gustavan T, Lovig Dahl H.the Water Barrier Function Of The Skin In Relation To The Water Content OfThe Stratum Corneum,ph And Skin Lipids. The Effect Of Alkaline Soap And Syndet Dey Skin In Elderly , Non Atopics Patients .*acta Derm Venerol* 1988; 68:277-83.